

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE



Applicant: George Treacy

Application No.: 09/942,075

Group Art Unit: 1644

Filed: August 28, 2001

Examiner: Nolan, P.

Confirmation No.: 6161

For: ANTI-TNF α ANTIBODIES IN THERAPY OF ASTHMA

CERTIFICATE OF MAILING OR TRANSMISSION	
I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, or is being facsimile transmitted to the United States Patent and Trademark Office on:	
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DECLARATION OF DON E. GRISWOLD, PH.D.
UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Don E. Griswold, Ph.D., declare and state that:

1. I have been employed at Centocor, Inc., 200 Great Valley Parkway, Malvern, PA 19355 since 2001, most recently as ~~Senior Director~~ and Head, Department of Immunobiology. I have been advised that Centocor is the assignee of the entire right, title and interest of the subject application.

2. I received my Ph.D. degree in Pharmacology from the University of Kansas Medical Center, Kansas City, Kansas in 1969. A copy of my curriculum vitae, which describes my educational and professional experience, is attached as Exhibit A.

3. I have published extensively in refereed publications, most of which have been focused in the areas of inflammation, immunopharmacology, and pulmonary and cutaneous pharmacology. A list of publications authored or co-authored by me is included as part of my curriculum vitae.

4. I have read the Office Action dated May 18, 2004, the Office Action dated August 21, 2003, and the art cited by the Examiner in the Office Actions, in particular the cited references of Konno *et al.* (*Int. Arch. Allergy Immunol.*, 105:308-316 (1994)), Shah *et al.* (*Clin. Exper. Allergy*, 25:1038-1044 (1995)), and Lukacs *et al.* (*J. Immunol.*, 154:5411-5417 (1995)). I have also read the patent application and the presently pending claims that were rejected in the Office Action.

5. Le *et al.*, U.S. Patent No. 5,698,195, discloses lung pathology generically, but does not disclose asthma.

6. Konno *et al.* examined the influence of roxithromycin (RXM), a macrolide antibiotic, and polyclonal rabbit anti-mouse TNF α antibodies on cytokine appearance in mouse lung extract induced by lipopolysaccharide (LPS) inhalation and on bronchial responsiveness (BR) to methacholine (Mch) in LPS-treated mice. Although inhalation of LPS causes pulmonary inflammatory responses and an increase in BR, it is not considered as an animal model for asthma. Thus, results obtained using the LPS mouse model would not provide evidence for the treatment of asthma.

7. Shah *et al.* summarize the scientific rationale available in 1995 that supported TNF α as an attractive target for asthma. In particular, Shah *et al.* report results showing (1)

increased levels of TNF α in sputum of patients with acute attacks of asthma; (2) increased number of cells expressing TNF α mRNA in bronchoalveolar lavage (BAL) fluid of stable atopic asthmatic subjects when compared to BAL of normal subjects; and (3) TNF α levels up to 20 times greater in BAL fluid of patients with symptomatic asthma than asymptomatic patients. From these results, Shah *et al.* concluded that "it appears that there is a disease related upregulation of TNF α which suggests that this cytokine plays a key role in ongoing airways inflammation" (page 1040, column 2, lines 6-8).

Shah *et al.* also report results indicating that TNF α may be associated with acquired airway hyperresponsiveness, a pathophysiological hallmark of asthma, and provided the scientific rationale available in 1995 that supported TNF α as an attractive target for asthma. However, Shah *et al.* do not disclose scientific data showing that blocking TNF α would treat asthma. Accordingly, Shah *et al.* do not provide evidence that would have taught one of ordinary skill in the art to effectively treat asthma or airway inflammation associated with in a human patient with an anti-TNF α antibody.

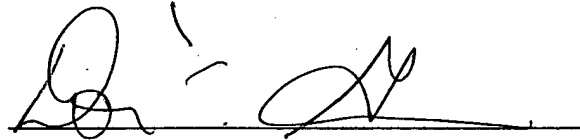
8. Lukacs *et al.* examined the role of TNF in the initiation and maintenance of leukocyte recruitment in airway inflammation induced by intratracheal challenge with soluble parasite (*Schistosoma mansoni*) egg Ag (SEA). The SEA-induced airway inflammation model used by Lukacs *et al.* is a model of Th2 cell-induced eosinophilic airway inflammation that allows for the study of the recruitment of various leukocyte subsets to lungs and airways. This model of airway inflammation has both an early neutrophilic (8-h) and a later (48-h) eosinophilic airway infiltration.

However, Lukacs *et al.* treated SEA-challenged mice with a TNF receptor antagonist (sTNFR-Fc), not with an anti-TNF α antibody. Since more than one cytokine can bind to TNFR, sTNFR-Fc is not as specific as a neutralizing anti-TNF α mAB. As a matter of fact, TNF receptor antagonists antagonize the activities of both TNF α and TNF β (lymphotoxin), whereas anti-TNF α antibodies do not neutralize the activity or effect of lymphotoxin.

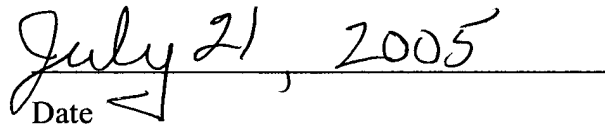
Thus, Lukacs *et al.* do not provide data that would have led one of ordinary skill in the art to conclude that administration of an anti-TNF antibody to a subject would be

effective in methods of treating asthma, in methods of treating airway inflammation associated with asthma, and in methods of reducing accumulation in lungs of inflammatory cells associated with asthma.

9. I declare that all statements made in this Declaration of my own knowledge are true and that all statements made on information and belief are believed to be true. Moreover, these statements are made with the knowledge that willful false statements and the like made by me are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

A handwritten signature in black ink, appearing to read 'Don E. Griswold', written over a horizontal line.

Don E. Griswold, Ph.D.

A handwritten date 'July 21, 2005' in black ink, written over a horizontal line. Below the line, the word 'Date' is printed with a small arrow pointing to the line.

Attachment

Exhibit A Curriculum vitae, including list of publications



CURRICULUM VITAE

Don E. Griswold, Ph.D.

November, 2004

ADDRESS: Centocor, Inc.
Department of Immunobiology
200 Great Valley Parkway
Malvern, PA USA 19355-1307

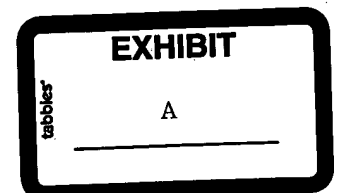
TELEPHONE: (610) 651-6994
FAX: (610) 240-4064

DATE AND PLACE OF BIRTH: June 24, 1943, Newton, Kansas

EDUCATION:

<u>Institution</u>	<u>Degree</u>	<u>Date Received</u>	<u>Major(s)</u>
University of Kansas Medical Center Kansas City, Kansas	Ph.D.	1969	Pharmacology
Emporia State University Emporia, Kansas	B.A.	1965	Microbiology and Chemistry

November, 2004



PROFESSIONAL EXPERIENCE:

CENTOCOR, INC.

Senior Director and Head, Department of Immunobiology (January 2001-Present)

I am currently directing efforts to discover and promote biological therapeutics with potential utility in the treatment of immune-mediated inflammatory disorders. In addition, support of collaborations among Centocor Research departments as well as J&J member companies involved in this area of research is on going.

SMITHKLINE BEECHAM PHARMACEUTICALS

Director, Department of Pulmonary Pharmacology (June 1998-December 2000)

I conducted and directed broad-based research in the areas of pulmonary and cutaneous pharmacology. My efforts involved the molecular biological and biochemical evaluation of mediators in different disease models. In addition, we developed *in vivo* models with the key feature of providing evidence of mechanism of action and proof of concept. This research was directed toward several disease targets including asthma, COPD, psoriasis, atopic dermatitis and eczema.

Associate Director, Department of Immunopharmacology (1994-1998)

I conducted and directed broad-based research in inflammation and immunopharmacology. My effort involved the search for inflammation-associated novel gene expression in different disease models and identification of human homologs. In addition, we developed both *in vitro* and *in vivo* models with the key feature of providing evidence of mechanism of action.

Assistant Director, Department of Inflammation and Respiratory Pharmacology. (1990-1994)

I coordinated inflammation research efforts and provided critical in vivo and/or in vitro model systems for several major strategic areas. We identified and brought forward development candidates in several of these areas.

Assistant Director, Department of Immunology. (1986-1990)

Initially as Deputy Director of the Inflammation and Arthritis Program, and later supervising that position, I coordinated a team of thirty scientists in the discovery and development of antiinflammatory and antiarthritic drugs. A unique class of antiinflammatory/antiarthritic agents (pyrroloimidazoles) was discovered and the lead compound was recommended for clinical development. Several compounds were identified for pre-development consideration. In addition, selective 5-LO agents were discovered and promoted as anti-asthmatic agents.

Senior Investigator, Department of Immunology. (1978-1986)

I supervised several associates and one Ph.D. and his staff in conducting in vitro and in vivo/ex vivo assays to measure the inhibition of leukotriene and prostanoid production. In addition, key model systems to differentiate lipoxygenase inhibitors from cyclooxygenase inhibitors were developed and adopted. Key findings were the immunoregulatory actions of Ridaura (auranofin), the action of histamine type-2 receptor antagonists on T suppressor cell function, and the characterization of the immunosuppressive effects of concanavalin A.

Associate Senior Investigator, Department of Pharmacology. (1974-1978)

I conducted adjuvant rat studies as a primary in vivo screen for antiarthritic agents. I also participated in the development of auranofin (Ridaura) and developed immunological models to explore the immunopharmacology of key compounds of interest. I had responsibility for the majority of the pharmacology conducted in the Arthritis and Immunoregulatory Research Mission.

BROWN UNIVERSITY

Division of Bio-Medical Sciences and Department of Medicine
Roger Williams General Hospital
Providence, RI

Assistant Professor (Research) of Medicine. (1973-1974)

I participated in fundamental cancer research. Our findings included demonstration of selective immunosuppression by cytostatic/cytotoxic drugs. I acted as advisor to 3 Masters of Medical Science students, lectured and conducted laboratory experiences for Brown University students.

University Instructor. (1971-1973)

I conducted research in cancer and immunopharmacology. I participated in teaching of Brown University students.

Research Fellow. (1969-1971)

I evaluated and developed methods to examine drug hypersensitivity and initiated work on immunoregulatory action of cytotoxic agents.

UNIVERSITY OF KANSAS MEDICAL CENTER

Department of Pharmacology
Rainbow Boulevard
Kansas City, Kansas

Graduate Student Laboratory Assistant. (1966-1969)

I was responsible for setup and conduct of the Pharmacology laboratory experience for medical students. I was also responsible for pharmacology lectures for nursing students.

EMPORIA STATE UNIVERSITY

Department of Microbiology
Emporia, Kansas

Research Assistant. (1963-1965)

I conducted research in microbiology and immunology and initiated research on assays of antibody-forming cells in amphibia (*Rana pipiens*). The work was presented at a regional meeting of the American Society for Microbiology.

HONORS, AWARDS, AND MEMBERSHIPS:

- Who's Who in Frontier Science and Technology Nomination Committee, Alfred P. Sloan Jr. Prize, General Motors Cancer Research Foundation
- Lambda Delta Lambda
- Sigma Xi
- American Association for Cancer Research
- American Association for the Advancement of Science
- New York Academy of Science
- American Society for Pharmacology and Experimental Therapeutics
- The Society for Investigative Dermatology
- American Thoracic Society
- Centocor Research Executive Committee Member
- J&J Immunologically-Mediated Inflammatory Disorders/Pulmonary Therapeutic Area Optimization Committee (TAOC) and Core TAOC Member

EDITORIAL RESPONSIBILITIES:

Inflammation Research
Cancer Research
Science
International Journal of Immunopharmacology
Expert Opinion on Therapeutic Patents
British Journal of Pharmacology
Journal of Pharmacology and Experimental Therapeutics
General Pharmacology, The Vascular System
American Journal of Respiratory and Critical Care Medicine

CONFERENCES AND SYMPOSIA ORGANIZED:

Workshop on Inflammation Models IRA 1994

INVITED PRESENTATIONS, SEMINARS AND SYMPOSIA:

Griswold, D.E. Pharmacology of Cytokine Suppressive Anti-Inflammatory Drugs / CSAID. Presented at SRI Conference entitled "On the Cutting Edge of Anti-Inflammatory Drug Discovery" New York, New York March 13-14, 1995.

Griswold, D.E. Pharmacology of an Emerging Dermatology Portfolio. Presented at Galderma, Paris, France, October 16, 1996.

Griswold, D.E. Pharmacology of an Emerging Dermatology Portfolio. Presented at LEO Pharmaceuticals, Copenhagen, Denmark, October 18, 1996.

Griswold, D.E. Pharmacology of an Emerging Dermatology Portfolio. Presented at Schering AG, Berlin, Germany, November 1, 1996.

Griswold, D.E. Pharmacology of CSBP/p38 Inhibitors. Presented to Department of Dermatology, University of Nijmegen, Nijmegen, The Netherlands. February 6, 1997.

Griswold, D.E. Pharmacology of MAP Kinase Inhibitors. Presented at IBC Conference entitled "New Drugs for Asthma." National Heart and Lung Institute, London, UK June 16 and 17, 1998.

Griswold, D.E. Pharmacology of p38 Kinase Inhibitors. Presented at an Imperial College Conference entitled "Conquering Airway Inflammation in the 21st Century", National Heart and Lung Institute London, UK September 14-16, 1998.

Griswold, D.E. Invited Lecture on Eicosanoid Pharmacology. Thomas Jefferson University. Oct 1, 1998.

Griswold, D.E. Institut Pasteur EuroConference on Chronic Lung diseases, talk entitled "Will antibodies have a role in the therapy of COPD?" Paris, France June 27-29, 2001

Griswold, D.E. Invited presentation to Groningen Research Institute for Asthma and COPD. Groningen, The Netherlands January, 2003

Griswold, D.E. Invited presentation to Professor Stephen Holgate and staff at University of Southampton, UK, July, 2003

Griswold, D.E. and Anuk Das. Invited presentation to Professor Peter Barnes and Trevor Hansel at National Heart and Lung Institute, London, UK, April, 2004

PATENTS:

1. U.S. Patent 4,686,231 issued August 11, 1987.
2. U.S. Patent 4,778,806 issued October 18, 1988.
3. U.S. Patent 4,780,470 issued October 25, 1988.
4. U.S. Patent 4,794,114 issued December 27, 1988.
5. U.S. Patent 5,134,150 issued July 28, 1992.
6. U.S. Patent 5,317,019 issued May 31, 1994.
7. U.S. Patent 5,824,696 issued October 20, 1998.
8. U.S. Patent 5,929,096 issued July 27, 1999.
9. U.S. Patent 5,981,538 issued November 9, 1999

PATENTS (continued)

10. U.S. Patent 6,759,410 issued July 6, 2004

PUBLICATIONS :

1. Griswold, D.E., and Uyeki, E.M.: Immunosuppressant effect of salicylates and quinine on antibody-forming cells. *Eur. J. Pharmacol.* 6:56-60 (1969).
2. Griswold, D.E., and Uyeki, E.M.: The effect of 5-fluorouracil on direct and developed spleen hemolysin plaque-forming cells in mice. *Tumori* 12:109-114 (1969).
3. Griswold, D.E., and Uyeki, E.M.: Quantitation of immediate hypersensitivity in various mouse strains. *Int. Arch. Allergy and Ap. Immun.* 40:682-690 (1971).
4. Griswold, D.E., Heppner, G.H., and Calabresi, P.: Selective suppression of humoral and cellular immunity with cytosine arabinoside. *Cancer Res.* 32:298-301 (1972).
5. Calabresi, P., Griswold, D.E., Poplin, E.A. and Heppner, G.H.: Selective immunosuppression by drugs in complex immune responses. *Pharmacology and the future of man. Proc. 5th Intl. Cong. Pharmacol.* 5:421-430 (1972).
6. Griswold, D.E., Heppner, G.H., and Calabresi, P.: Alteration of immunocompetence by mammary tumor virus. *J. Natl. Cancer Inst.* 50:1035-1038 (1973).
7. Laing, C.A., Griswold, D.E., and Heppner, G.H.: A new method for the quantitation of tumor growth in situ: Measurement by plethysmography. *J. Natl. Cancer Inst.* 51:1345-1348 (1973).
8. Mourachian, H., and Griswold, D.E.: A method for permanently recording micro-hemagglutination patterns. *J. Immunol. Meth.* 4:29 (1974).

9. Griswold, D.E., DiLorenzo, J.A., and Calabresi, P.: Quantitation and pharmacological dissection of oxazolone-induced contact sensitivity in the mouse. *Cellular Immunol.* 11:198-204 (1974).
10. Griswold, D.E., and Calabresi, P.: Human leukocyte reactivity to penicilloylated erythrocytes. *Blood* 44:501-509 (1974).
11. DiLorenzo, J.A., Griswold, D.E., Bareham, C.R., and Calabresi, P.: Selective alteration of immunocompetence with methotrexate and 5-fluorouracil. *Cancer Res.* 34:124-128 (1974).
12. Bareham, C.R., Griswold, D.E., and Calabresi, P.: Synergism of methotrexate with Imuran and with 5-fluorouracil and their effects on hemolysin plaque-forming cell production in the mouse. *Cancer Res.* 34:571-575 (1974).
13. Medina, D., Stockman, G., and Griswold, D.E.: Significance of chemical carcinogen-induced immunosuppression in mammary tumorigenesis in Balb/c mice. *Cancer Res.* 34:2663-2668 (1974).
14. Heppner, G.H., Griswold, D.E., DiLorenzo, J.A., Poplin, E.A., and Calabresi, P.: Selective Immunosuppression by Drugs in Balanced Immune Responses. *Fed. Proc.* 33:1882-1885 (1974).
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16. Griswold, D.E., Kropp, J.S., Manning, J.S., and Heppner, G.H.: Correction of a murine mammary tumor virus associated immunological depression by selective immunosuppression with cytosine arabinoside. *Cancer Res.* 35:2670-2674 (1975).
17. Griswold, D.E. and Walz, D.T. : Condition-dependent immunoregulatory control of contact sensitivity by levamisole. *Inflammation* 2:277-284 (1977).
18. Griswold, D.E. and Walz, D.T.: Restoration of methotrexate-suppressed oxazolone-induced contact sensitivity with levamisole. *Inflammation* 3:111-116 (1978).

19. Walz, D.T., and Griswold, D.E.: Immunopharmacology of gold sodium thiomalate and auranofin (SK&F D-39162): Effects on cell-mediated immunity. *Inflammation* 3:117-128 (1978).
20. Walz, D.T., Griswold, D.E., DiMartino, M.J., and Bumbier, E.E.: Distribution of gold in blood following administration of auranofin (SK&F D-39162). *J. Rheumatol.* 6:56-60 (1979).
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22. Walz, D.T., Griswold, D.E., DiMartino, M.J. and Bumbier, E.E.: Pharmacokinetics of gold following administration of auranofin (SK&F D-39162) and myochrysine to rats. *J. Rheumatol.* 7:820-824 (1980).
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27. Walz, D.T., DiMartino, M.J., and Griswold, D.E.: Comparative pharmacology and biological effects of different gold compounds. *J. Rheumatol.* 9:54-60 (1982).
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52. Lee, J.C., Griswold, D.E., Votta, B., and Hanna, N.: Inhibition of monocyte IL-1 production by the antiinflammatory compound, SK&F 86002. *Intl. J. Immunopharmacol.* 10:835-843 (1988).
53. Griswold, D.E., Hillegass, L.M., Meunier, P.C., DiMartino, M.J., and Hanna, N.: Effect of inhibitors of eicosanoid metabolism in murine collagen-induced arthritis. *Arth. Rheum.* 31:1406-1412 (1988).
54. Griswold, D.E., Hillegass, L.M., Hill, D.E., Egan, J.W. and Smith, E.F. III: Method for quantification of myocardial infarction and inflammatory cell infiltration in rat cardiac tissue. *J. Pharmacol. Meth.* 20:225-235 (1988).

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